REMARKS

Claims 1-18 remain pending in the present application. Claims 1-7 and 13-15 are under examination, claims 8-12 and 16-18 having been withdrawn from consideration as drawn to non-elected inventions. Claims 1-3, 6, 7, and 13 are amended above to clarify their intended scope. The amendments are generally supported throughout the specification and in the claims as originally filed. More specifically, support for amended claims 1-3 is found, for example, at page 10, lines 21-23; page 11, lines 11-24; page 7, lines 10-13; page 14 lines 16-18. Support for amended claims 6 and 7 is found in the specification at page 6, lines 7-13. Support for the "two-chain antibodies" term in claims 1, 2, 6 and 7 is implicit throughout the specification, e.g., in the carryover paragraph of pages 5-6, which explains that the displayed antibodies are composed of both a heavy chain and a light chain (i.e., are two-chain antibodies), and at page 12, lines 24-29, which explains that the heavy chain is associated with the light chain fusion protein presented on the phage particle.

No new matter has been added.

Applicant requests entry of the above amendment and allowance of the claims in view of the remarks in this Response.

Information Disclosure Statement

Applicant thanks the Examiner for entry of the reference cited in the IDS of May 15, 2006. The Examiner has stated that although the Applicant reported that an IDS for this application was filed on September 13, 2005, she does not see such an IDS entry on the record. The Applicant notes that the US Patent and Trademark Office mistakenly entered that Information Disclosure Statement in a different case, U.S. Application Serial No. 10/510,971, rather than in the present case. Thus, on January 22, 2008, the Applicant resubmitted the references A3-A8 that were on the PTO-1449 form and requested that they be made of record in the present case. The Applicant further notes that the Information Disclosure Statement filed on January 22, 2008 incorrectly referenced the date of the previously filed Information Disclosure Statement as December 13, 2005. A communication was submitted to the US Patent and

Trademark Office on February 11, 2008 acknowledging the error and apologizing for any resulting confusion. Applicant respectfully requests that the Examiner initial the PTO-1449 form that was submitted on January 22, 2008.

Objection to the Drawings

The Examiner objected to the Replacement Sheets containing the corrected drawing figures for Figures 1 and 2 because a marked-up copy of the Replacement Sheets was not included in the amendment filed July 7, 2006. Applicant has submitted the marked-up copies of each Replacement Sheet, that is, Figures 1 and 2. Also submitted for the Examiner's convenience is a clean copy of the set of Replacement Sheets that was filed on July 7, 2006. For clarity, each change in the Replacement Drawings relative to the informal Drawings submitted at the time the application was filed is labeled with a number within a triangle. The corresponding explanation of each change is shown below.

Figure 1

1) The black oval originally representing the CH1 region of the Fd heavy chain was changed in the replacement drawing to a vertically striped oval.

2) The black oval originally representing the CL region of the light chain was changed in the replacement drawing to a cross-hatched oval.

3) The diagonally-striped oval originally representing the VL region of the light chain was changed in the replacement drawing to a horizontally-striped oval.

4) The black oval originally representing the CH1 region of the heavy chain was changed in the replacement drawing to a vertically striped oval.

5) The black oval originally representing the CL region of the light chain was changed in the replacement drawing to a cross-hatched oval.

6) The diagonally-striped oval originally representing the VL region of the light chain was changed in the replacement drawing to a horizontally-striped oval.

Figure 2

1) The black rectangle originally representing the first host cell was changed in the replacement drawing to a white rectangle.

2) The black oval originally representing the CH1 region of the Fd heavy chain was changed in the replacement drawing to a vertically striped oval.

3) The black oval originally representing the CL region of the light chain was changed in the replacement drawing to a cross-hatched oval.

4) The diagonally-striped oval originally representing the VL region of the light chain was changed in the replacement drawing to a horizontally-striped oval.

5) The black oval originally representing the CH1 region of the Fd heavy chain was changed in the replacement drawing to a vertically striped oval.

6) The black oval originally representing the CL region of the light chain was changed in the replacement drawing to a cross-hatched oval.

7) The diagonally-striped oval originally representing the VL region of the light chain was changed in the replacement drawing to a horizontally-striped oval.

8) The shaded arrows originally depicting the order of the method steps were changed in the replacement drawing to white arrows.

9) The solid oval originally depicting the antibodies displayed on the surface of the phage captured on the left in the "Panning with AR1" step was changed in the replacement drawing to a white oval.

10) The solid oval originally depicting the antibodies displayed on the surface of the phage captured on the right in the "Panning with AR1" step was changed in the replacement drawing to a white oval.

11) The black oval originally representing the CH1 region of the Fd heavy chain was changed in the replacement drawing to a vertically striped oval.

12) The black oval originally representing the CL region of the light chain was changed in the replacement drawing to a cross-hatched oval.

13) The diagonally-striped oval originally representing the VL region of the light chain was changed in the replacement drawing to a horizontally-striped oval.

14) The black rectangle originally representing the second host cell was changed in the replacement drawing to a white rectangle.

15) The black oval originally representing the CH1 region of the Fd heavy chain was changed in the replacement drawing to a vertically striped oval.

16) The black oval originally representing the CL region of the light chain was changed in the replacement drawing to a cross-hatched oval.

17) The diagonally-striped oval originally representing the VL region of the light chain was changed in the replacement drawing to a horizontally-striped oval.

18) The black oval originally representing the CH1 region of the Fd heavy chain was changed in the replacement drawing to a vertically striped oval.

19) The black oval originally representing the CL region of the light chain was changed in the replacement drawings to a cross-hatched oval.

20) The diagonally-striped oval originally representing the VL region of the light chain was changed in the replacement drawing to a horizontally-striped oval.

21) The solid oval originally depicting the antibodies displayed on the surface of the phage captured on the left in the "Panning with AR2" step was changed in the replacement drawing to a white oval.

22) The solid oval originally depicting the antibodies displayed on the surface of the phage captured on the right in the "Panning with AR2" step was changed in the replacement drawing to a white oval.

23) The black oval originally representing the CH1 region of the Fd heavy chain was changed in the replacement drawing to a vertically striped oval.

24) The black oval originally representing the CL region of the light chain was changed in the replacement drawing to a cross-hatched oval.

25) The diagonally-striped oval originally representing the VL region of the light chain was changed in the replacement drawing to a horizontally-striped oval.

26) The black ovals originally representing the CH3 regions of the heavy chains were changed in the replacement drawing to vertically striped ovals.

27) The black ovals originally representing the CH2 regions of the heavy chains were changed in the replacement drawing to vertically striped ovals.

28) The black ovals originally representing the CH1 regions of the heavy chains were changed in the replacement drawings to vertically striped ovals.

29) The black ovals originally representing the CL regions of the light chains were changed in the replacement drawing to cross-hatched ovals.

30) The diagonally-striped ovals originally representing the VL regions of the light chains were changed in the replacement drawing to horizontally-striped ovals.

31) The white oval originally representing the VH region of the heavy chain was changed in the replacement drawing to a black oval.

35 U.S.C. §102e

Claims 1, 2, 4-7, 14 and 15 stand rejected under 35 U.S.C. §102(e) as anticipated by Winter et al. (US2004/0219643). According to the Office Action on page 6, "The method inventions for screening bi-specific antibodies produced from the same light chain (or VL) library are anticipated by Winter." The Office Action continues:

> Winter teaches method steps for producing the antibodies: a) selecting a first variable domain (VH1) by its ability to bind to a first epitope expressed from a phage display library, b) selecting a second variable region (VH2) by its ability to bind to a second epitope expressed from a phage display library, c) combining any one of the selected VH regions into a construct with a library of light chains or VL domains for expression by the same host; and d) selecting the dual specific ligand or multimer by its ability to bind to the first and second epitopes recognized by the VH domains (or the ability of the light chains to bind to an antigen). The technology of Winter allows one of ordinary skill in the art to create and screen various kinds of libraries that are encompassed by the instant claimed method. One of ordinary skill in the art could produce any host cell secreting a selected heavy chain, introducing a light chain or VL library into the

> host cell, preparing a phage library presenting the antibodies constituted by the heavy and light chains or the VH and VL domains, and a library which is selected that presents the antibodies uniquely binding with the desired antigen. Thus the methods of Winter read on the method of the instant claims. (*Office Action at pages 7-8.*)

The Office Action concludes:

> Winter specifically discloses multimeric antibodies that could comprise dual specific heavy chains or VH domains while sharing the same light chain or VL domain (*i.e.*, anti-beta galactosidase). One skilled in the art following the methods of Winter could produce not only a bispecific antibody having VH and VL domains which recognized separate and distinct antigens, but multimers where the antibody shared the same VL domains but different VH domains, and which were produced from the same light chain library. (*Office Action at page 8.*)

Applicant respectfully traverses this rejection. As discussed below, the Office has failed to establish that each and every claim limitation is found in the cited art.

Claim 1 claims a screening method that has five explicit steps (a) through (e), each of which must be found in the reference in order to make out a proper anticipation rejection.

(a) The claimed method begins with host cells that secrete a heavy chain derived from an antibody that binds to a desired antigen (for purposes of this discussion, "antigen A").

(b) A phage library encoding a plurality of different light chains is introduced into the host cells. The cells then secrete phage that display two-chain antibodies on their surfaces, each antibody having one of the light chains (typically fused to a phage protein at the surface of the phage) associated with the single type of heavy chain produced by the host cells. Thus, at this point the heavy chain in each of the displayed two-chain antibodies is invariant, because the only available heavy chain is the one produced by the host cells, while the light chain varies from phage to phage.

(c) Phage displaying two-chain antibodies that bind to antigen A are selected, producing a sub-library of phage encoding light chains that bind antigen A when they are paired with the A-specific heavy chain produced in the host cells.

(d) This sub-library is then introduced into another set of host cells, these cells secreting a second heavy chain that binds to a second antigen, *e.g.*, antigen B. Each phage produced by these cells expresses a two-chain antibody composed of the phage's encoded light chain (which varies from phage to phage) in association with the single, B-specific heavy chain.

(e) Selecting for phage of step (d) that bind to antigen B results in a sub-library of phage encoding light chains that bind to antigen B when paired with B-specific heavy chain. Since the light chains encoded by these phage were previously selected for ability to bind to antigen A when paired with an A-specific heavy chain (see step (c)), the sub-library resulting from step (e) encodes antibody light chains that can pair cooperatively with either of these heavy chains to bind the heavy chain's respective cognate antigen.

The Examiner has not explained where she finds in Winter a disclosure of such a method, and applicants do not see it. Applicants first address what the Office action describes in the carryover paragraph of pages 7-8 as being the "Winter technology" (though it is not clear from what part of Winter the Office derives this description), and then, for completeness, address other methods that are explicitly set forth in Winter.

The "method steps" ascribed to Winter on pages 7-8 of the Office action are markedly different from the claimed method. For example, it appears from the description in the Office action that Winter did not utilize cells secreting a heavy chain as host cells for infection with a phage library encoding antibody light chains, as required by steps (a) and (b) of claim 1. Instead of carrying out steps (a) and (b) of claim 1 to produce phage expressing a two-chain antibody (with the heavy chain supplied by the host cells and the light chain supplied by the phage), Winter (according to the Office action) produced a library of constructs encoding single-chain antibodies, each construct containing sequence encoding (i) a heavy chain variable domain specific for a first epitope, and (ii) the variable domain of any of a variety of light chains, and introduced those constructs into phage for display and selection for binding to the first epitope. Winter then (according to the Office action) created a second such single-chain antibody library, substituting the heavy chain variable domain with a second one specific for a different epitope. From the description of Winter's disclosure set forth in the Office action, it thus appears that

Winter did not employ a two-chain antibody phage display method, as required by steps (b), (c), (d), and (d). Furthermore, there is no suggestion that Winter used host cells secreting a heavy chain as a means to supply the invariant heavy chain portion of the phage-displayed antibody, as required by steps (a), (b), and (d) of claim 1. Winter wouldn't have needed to do so, because (at least according to the Office action) he designed his phage to encode single-chain Fv containing, in a single polypeptide chain, both a heavy chain variable domain and a light chain variable domain. In addition, the Office action does not suggest that Winter took a phage library selected for binding to the first antigen and introduced it into cells to produce phage that were then selected on the second antigen, as required by step (d) of claim 1. Instead of such a sequential method, Winter's selections on different antigens (at least as described in the Office action) were apparently done in parallel: he had to do his selection on the second antigen with an entirely separate phage library encoding new scFv with the same mix of light chain domains but a different heavy chain variable domain. The presently claimed method is therefore quite distinct from Winter's, assuming that the Examiner has accurately described a method she found somewhere in Winter.

In saying that Winter's methods (as described in the Office action) "read on the method of the instant claims," the Examiner unfortunately misapprehends the proper standard for anticipation. Rather than point out where Winter meets the limitations of claim 1 by disclosing use of host cells secreting a heavy chain, and introducing a light chain phage library into such cells, and using the phage resulting from a screen of that library to infect other host cells secreting a different heavy chain, the Office action describes Winter's very different method and then attempts to bridge the gap between that and applicant's method by stating,

> The technology of Winter allows one of ordinary skill in the art to create and screen various kinds of libraries that are encompassed by the instant claimed method. One of ordinary skill in the art could produce any host cell secreting a selected heavy chain, introducing a light chain or VL library into the host cell, preparing a phage library presenting the antibodies constituted by the heavy and light chains or the VH and VL domains, and a library which is selected that presents the antibodies uniquely binding with the desired antigen. Thus the methods of Winter read on the method of the instant claims. *(Emphasis added)*

This, of course, misses the point: the question is not whether "the technology" of Winter "allows" one of ordinary skill in the art to create and screen the "kinds" of libraries that are encompassed by the claimed methods, but rather whether Winter in fact disclosed a method that meets all limitations of applicant's claims. Nor is it relevant that one of ordinary skill in the art "could produce" the host cell secreting a selected heavy chain, as specified in the present claims, and "could" have introduced a light chain library into it, and "could" have screened it. If Winter didn't explicitly disclose the methods within the four corners of his disclosure, there is no anticipation, regardless of what the Examiner speculates one "could" do.

If the Examiner intends to maintain this rejection, she is asked to point out exactly where in Winter the method attributed to Winter in the carryover paragraph of pages 7-8 of the Office action supposedly can be found, and also how this method as disclosed in Winter meets each of the limitations of claim 1, so that Applicants can reply appropriately.

For completeness, Applicants now address Winter's disclosure directly, rather than as filtered through the Office action. Applicants focus on the working examples in Winter, in particular the screening methods set forth in Examples 1 and 5.

Example 1 of Winter (beginning at paragraph [0180]) describes a method used to select a "dual specific" sc-Fv antibody directed against human serum albumin (HSA) and β-galactosidase (β-gal). Winter prepared two separate scFv libraries, one encoding scFv containing a variety of VL domains linked to a single "dummy" VH domain, and the second encoding scFv containing a variety of VH domains linked to a single "dummy" VL domain. The first library was screened against β-gal to select β-gal-binding VL domains. The second library was screened against HSA to select HSA-binding VH domains. The set of selected VL domains and the set of selected VH domains were then combined into a new library of scFv (without the "dummy" domains). That new scFv library was screened to identify scFv that bind to both antigens.

Clearly Example 1 of Winter does not disclose a method that meets the criteria of claim 1. For one thing, Winter's libraries contained phage that express scFv, not phage that express light chains as required by claim 1. Winter's Example 1 also does not disclose use of host cells that secrete a heavy chain, as required by claim 1, and so certainly does not disclose

introducing an antibody light chain library into such cells to cause secretion of phage libraries presenting two-chain antibodies composed of the heavy chain and a light chain, as required by claim 1.

Furthermore, Winter's purpose was to generate a "dual specific" scFv antibody in which the VL is directed against one antigen and the VH is directed against a second antigen, so that the scFv can simultaneously bind both antigens. Such a purpose would not have been served by applicant's screening method. In applicant's method, a light chain is selected for its ability to act as a "common" light chain able to associate with different heavy chains and thereby facilitate the antigen binding of those heavy chains to their cognate antigens. Applicant's method would not particularly select for a VL that, when put into an scFv with a VH, would permit the scFv to bind to the VL's cognate antigen as well as the VH's cognate antigen. Thus, Applicant's method not only was not disclosed by Winter, but also would not even accomplish Winter's purpose.

Example 5 of Winter is even less relevant than Example 1 to the presently claimed methods. Example 5 (beginning at paragraph [0200]) discloses a method for selecting "single domain antibodies." In this method, a phage library encoding only VH domains (i.e., with no VL domains present) was screened for binding to a particular antigen, APS. Separately, a second phage library encoding only VL domains (i.e., with no VH domains present) was screened for binding to β-gal. Neither of these screens utilized a host cell secreting a heavy chain, as required by the present claims. Nor did either employ a step of introducing phage encoding light chains into host cells, or screening the resulting two-chain antibodies displayed on the phage for binding to the heavy chain's cognate antigen. Thus, Example 5 also does not anticipate any of the present claims.

The Office action points to Winter's Examples as disclosing antibodies that "have in common the same VL domain or light chain for anti-beta galactosidase." Office action at page 7. (This appears to be a reference to, e.g., Example 3, which discloses three different scFv containing a common VL domain but different VH domains.) The Office action goes on to say "Hence a multimer of Winter could comprise a molecule having the same two or shared VL

domains paired with two VH domains against different antigens, and which would read on the intended antibody produced by the instant method." *(Emphasis added.)*

Applicant submits that such a conclusion reflects a fundamental misunderstanding of the law regarding anticipation. The present claims are not drawn to antibodies, multimeric or otherwise. The question to be asked is not whether Winter disclosed an antibody identical to one produced by the presently claimed methods, much less whether Winter disclosed an antibody that, in the Examiner's expansive view, "could" have the same domains that "could" be produced by the present methods. Rather, the appropriate question is whether Winter disclosed a screening method that precisely meets all of the limitations of the present claims. As demonstrated above, the answer to that is emphatically "no". Furthermore, contrary to the statement in the Office action at the bottom of page 8,[1] no "light chains (or VL) directed to different antigens as taught by Winter" could possibly "fall within the scope of the instant claims," for the simple reason that the instant claims are drawn to methods, not light chains.

Withdrawal of the rejection of claim 1 and its dependents for anticipation over Winter is respectfully requested.

Claim 2, the only other independent claim, is similar to claim 1 except with respect to the description of the second heavy chain in step (d). In claim 1, the second heavy chain is defined as binding to a desired antigen different from the antigen of step (a), while in claim 2, the second heavy chain is defined as comprising an amino acid sequence different from that of the heavy chain of step (a). The same arguments regarding the deficiencies of Winter detailed above apply to the rejection of claim 2 for anticipation. Accordingly, the rejection of claim 2 (and its dependents) as anticipated by Winter is plainly not warranted, and should be withdrawn.

35 U.S.C. §103

Claims 1-3 and 13 stand rejected under 35 U.S.C. §103 as obvious over Winter in view of Goldstein et al., J.Immunology 158: 872-879 (1997). According to the Office Action at page 10, "Winter appreciates forming heavy chains from antibody fragments but does not specifically

[1] "Thus light chains (or VL) directed to different antigens as taught by Winter than (sic) those to which the first and second heavy chains are directed fall within the scope of the instant claims."

disclose a Fd, and Goldstein specifically rectifies this deficiency. Goldstein is cited for showing the utility of Fd fragments in generating recombinant antibodies." The Office Action continues:

> One skilled in the art would have been motivated to have produced a method for screening commonly shared light chains in a bispecific antibody where the heavy chain was a Fd on the basis of the combined disclosure of Winter and Goldstein. Winter provides the motivation for making improved bispecific antibodies and methods for producing these molecules, and given the desirability of using smaller sized fragments that retain the full binding characteristics of the parent antibody, one skilled in the art would have been motivated to have used an Fd fragment as taught by Goldstein, because Goldstein teaches fusion methods, assembly of the Fd fragment with the light chain, and antigen specificity for the fragment upon assembly. One skilled in the art would have been reasonably assured of success in producing a screening method based on these disclosures because the technology was available to perform the steps to produce each of the different molecules on a step-wide basis according to the instant claimed method, and because bispecific antibodies sharing a common light chain were already known in the art based on the disclosure of Winter and that Fd fragments could be used in bispecific fusion proteins which resulted in successful assembly of the antibody into a functional, antigen-binding fragment based on Goldstein. *(Office Action at page 10.)*

The Examiner concludes: "Because Winter's results are unexpected and the antibodies are shown to work, one skilled in the art would have been reasonably assured of success in practicing any method steps of Winters that read on the instant method claim scope." *(Office Action at page 11.)*

Applicant traverses this rejection. The rejection is premised on the assumption that Winter discloses the methods of independent claims 1 and 2. As explained above, Applicant can find no disclosure in Winter of the methods as specified in claims 1 and 2, and the Examiner has not explained where Applicant's methods are disclosed. The mere fact that the Examiner believes that one "could" use various libraries of Winter to carry out methods the Examiner believes "could" end up producing antibodies that the Examiner believes "could" also have resulted from carrying out Applicant's claimed method is a far cry from establishing that the

claimed methods are disclosed in, or even obvious in view of, Winter.[2] Goldstein does not rectify these glaring deficiencies of Winter, and indeed is cited solely for its disclosure that Fd fragments have utility in generating recombinant antibodies.

Accordingly, the Examiner has not established that Winter and Goldstein, either alone or in combination, teach or suggest *all the limitations of the subject matter now claimed.* Nor do these references provide any motivation to modify each others' teachings to arrive at the presently claimed inventions. They disclose methods entirely different from Applicant's, carried out for different reasons. In view of the foregoing, the Office is respectfully asked to reconsider and withdraw this ground for rejection.

Applicant notes for the record that the Office action at page 11 states "THIS ACTION IS MADE FINAL," though the on Office Action Summary at page 1 of the Office Action, box 2b (indicating that the action is non-final) was marked. In a telephone conference with the undersigned on October 9, 2007, the Examiner acknowledged that the statement at page 11 was an error, and the Office Action is intended to be non-final.

Applicant submits that the claims are now in condition for allowance, and such action is requested. A petition for extension of time is being filed herewith. Please charge any required fees or credits to Deposit Account 06-1050, referencing attorney docket no. 14875-148US1.

[2] And even if the Examiner's novel interpretation of the law were the correct one, Applicant points out that Winter's libraries encoded VL or VH, not light chains as required by the present claims, so of course could not yield a molecule identical to one selected by the claim 1 method.

Respectfully submitted,

Date: April 2, 2008

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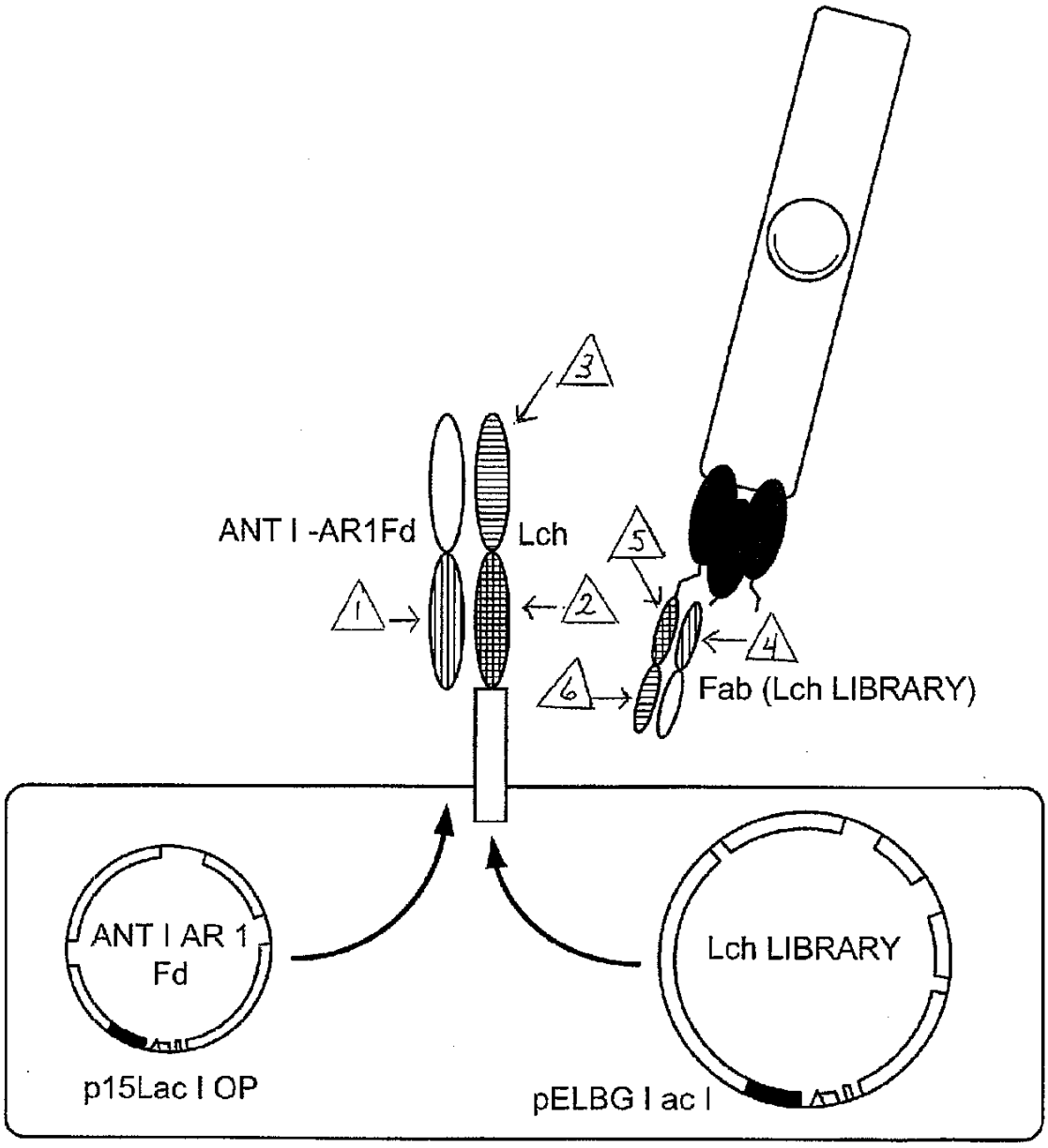
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Lch
1
2
3
4
5
6
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ANT I AR 1
Fd
p15Lac I OP
Lch LIBRARY
pELBG I ac I

FIG. 1

Annotated Sheet Showing Change(s)

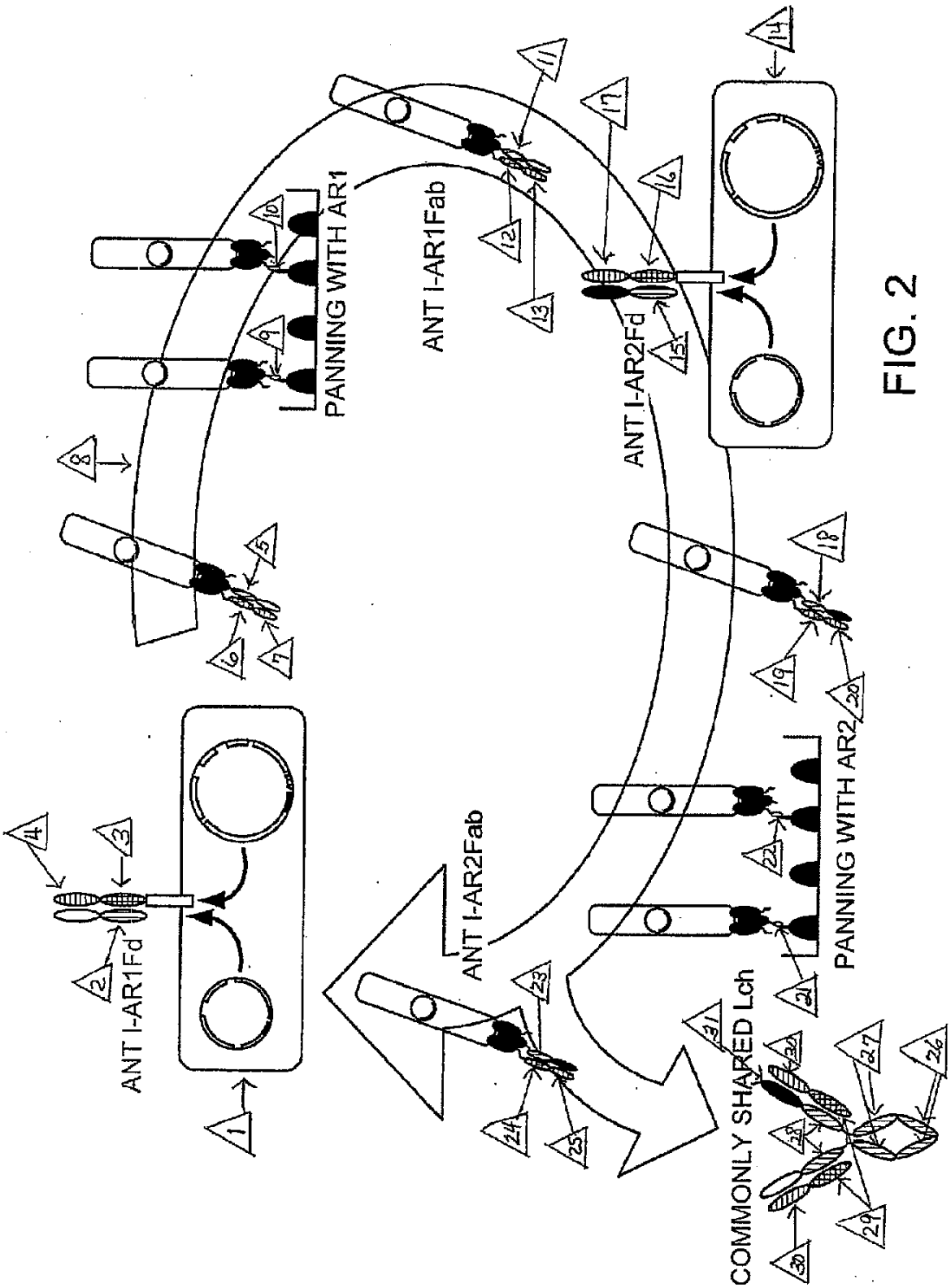
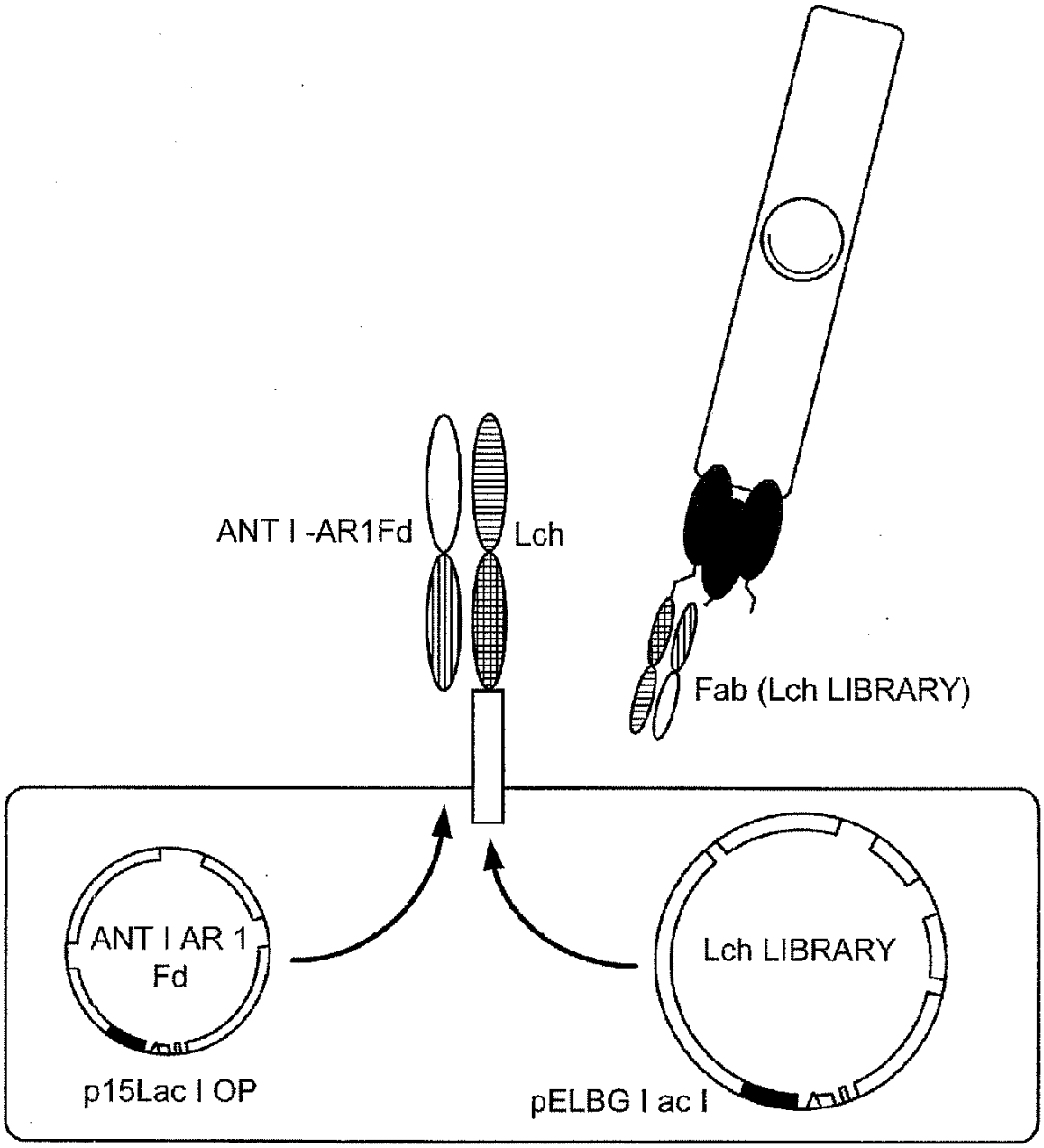


FIG. 2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Lch
Fab (Lch LIBRARY)
ANT I AR 1
Fd
p15Lac I OP
Lch LIBRARY
pELBG I ac I

FIG. 1

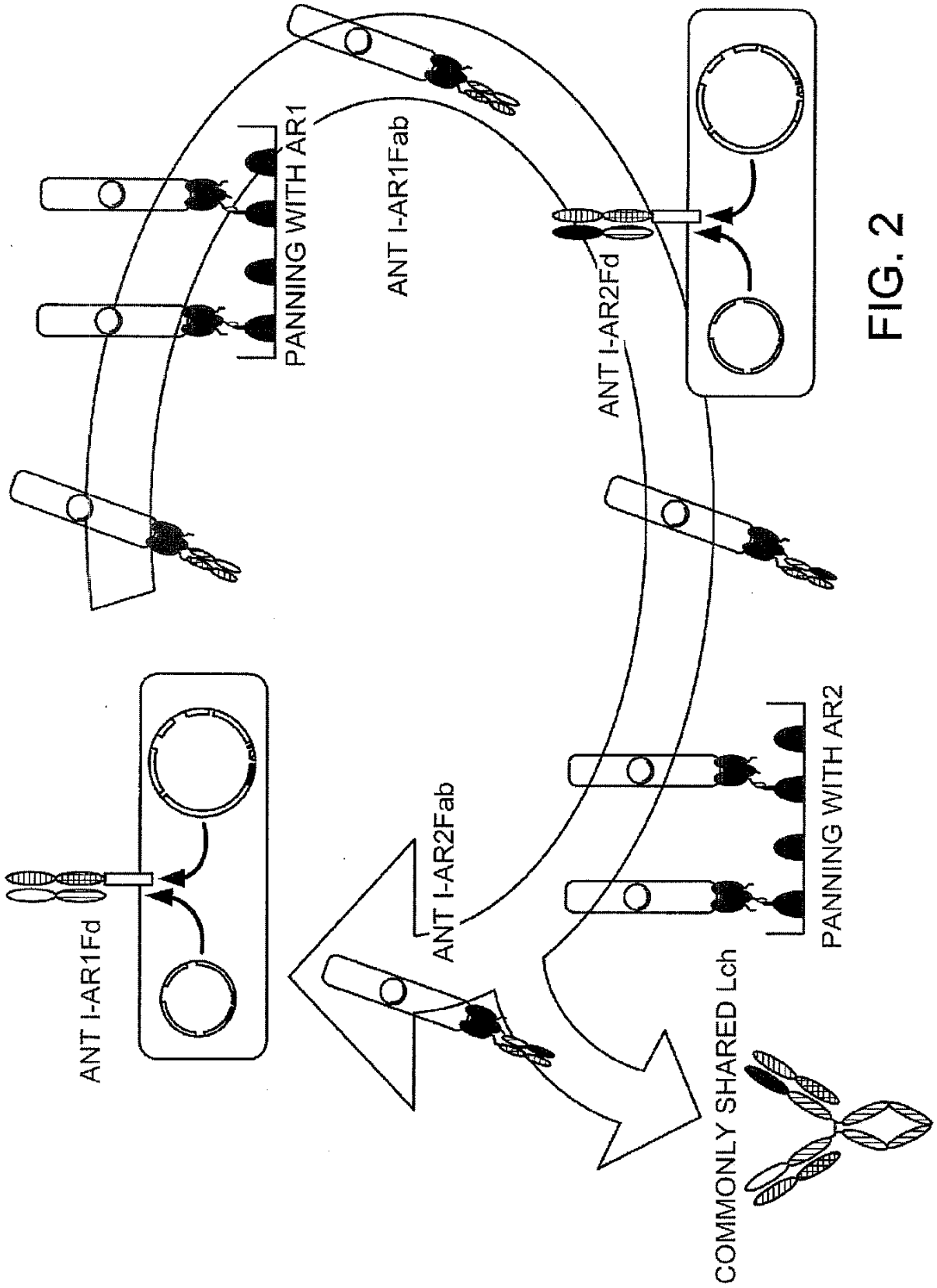
ANT I-AR1Fd
PANNING WITH AR1
ANT I-AR1Fab
ANT I-AR2Fd
ANT I-AR2Fab
PANNING WITH AR2
COMMONLY SHARED Lch

FIG. 2